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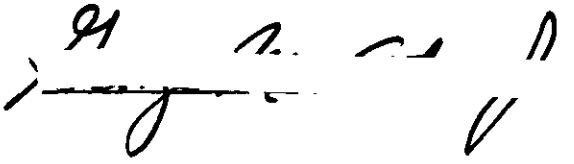

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REACTIONS OF N-SULFONYLAMINES

A THESIS

Presented to

The Faculty of the Graduate Division

by

George Milton Atkins, Jr.

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

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REACTIONS OF N-SULFONYLAMINES

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GLOSSARY OF ABBREVIATIONS

CT	column temperature.
DME	1,2-dimethoxyethane.
DMSO	dimethylsulfoxide.
GLC	gas-liquid chromatography.
HFR	helium flow rate.
Hz	hertz.
ppm	parts per million.
RT	retention time.
THF	tetrahydrofuran.
tlc	thin-layer chromatography.
TMS	tetramethylsilane.

CHAPTER I

INTRODUCTION

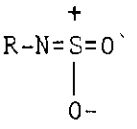
Heterocumulenes are olefinic compounds possessing adjacent π-bonds in which one or more of the atoms in the π-system are hetero atoms, such as oxygen, nitrogen or sulfur. Interest in the chemistry of heterocumulenes has increased steadily since the introduction of isocyanates into the literature over a century ago (1). Today over two dozen heterocumulenes are known. Several heterocumulenes containing sulfur as the central atom are shown in Table 1.

Table 1. Some Heterocumulenes Containing Sulfur

S^{VI}	S^{IV}
$R_2C{=}\overset{+}{S}{=}O$ (O$^-$), sulfenes	$R_2C{=}S{=}O$, sulfines
$R{-}N{=}\overset{+}{S}{=}O$ (O$^-$), N-sulfonylamines (I)	$R{-}N{=}S{=}O$, N-sulfinylamines
$O{=}\overset{+}{S}{=}O$ (O$^-$), sulfur trioxide	$O{=}S{=}O$, sulfur dioxide

The studies reported in this thesis are concerned with the synthesis of a new heterocumulene, the N-sulfonylamines (I), the only

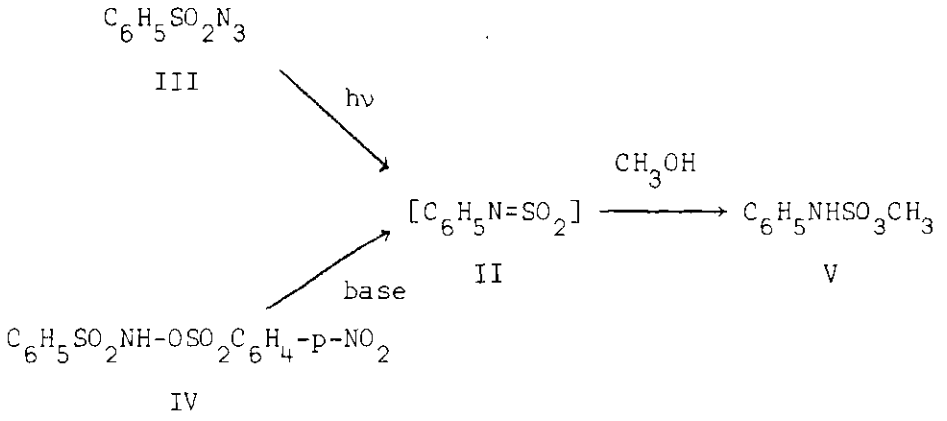
compounds in Table 1 which had not been prepared previously. Isoelectronic with sulfenes and otherwise closely related to N-sulfinylamines,



I

N-sulfonylamines* might be expected to show similar reactivity or stability.

Only a few literature references to N-sulfonylamines may be found. N-sulfonylaniline (II) has been proposed as an intermediate



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*The names *sulfurylamine* (2) and *azasulfene* (3) have been ascribed to structure I. However, *N-sulfonylamine* is the name currently preferred and used for indexing by the Chemical Abstracts Service and is more consistent with the naming of related heterocumulenes.

The author is grateful to Dr. K. L. Loening, Director for Nomenclature of the Chemical Abstracts Service, for his assistance in naming several of the compounds described in this thesis.

in the Curtius and Lossen rearrangements of benzenesulfonylazide (III) and N-p-nitrobenzenesulfonoxybenzenesulfonamide (IV), respectively. In both cases, the interposition of II was inferred since the rearrangements provided methyl N-phenylsulfamate (V) when methanol was used as the solvent (2).

A recently reported attempt to prepare N-sulfonylaniline involved the photolysis of phenylazide in the presence of sulfur dioxide (3). However, the intermediate phenylnitrene (VI) apparently did not add sulfur dioxide, and the products isolated resulted from the reaction of VI with the solvent.

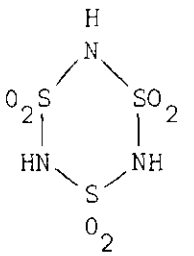
$$C_6H_5N_3 \xrightarrow{h\nu} C_6H_5\ddot{N}: \xrightarrow[C_6H_6]{SO_2} II$$

VI

It has been reported that when ammonia is passed into an anhydrous solution of sulfur trioxide in nitromethane approximately one-fourth of the sulfur trioxide is converted into sulfimide* (VII). The evidence for

$HN{=}SO_2$

VII

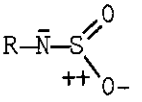


VIII

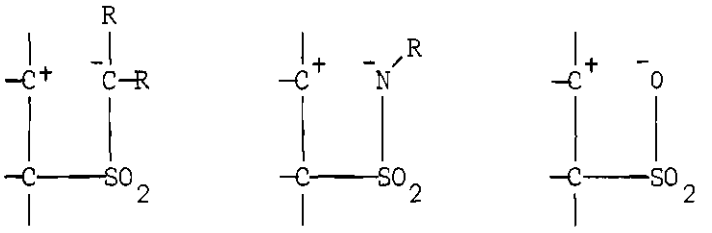
*Sulfimide might be named *N-sulfonylamine* as the parent compound of the series. However, the term *sulfimide* is well known and will be used herein.

the intervention of VII was the isolation of polymers $(HNSO_2)_X$ from the nitromethane solution, one of which was the cyclic trimer VIII (4).

One reason for the interest in heterocumulenes has been the ability of several members of this class to undergo cycloaddition reactions (5). N-Sulfonylamines might be expected to participate in non-concerted cycloaddition reactions (a property which can be attributed to both sulfenes and N-sulfinylamines) due to a polarization of the nitrogen-sulfur multiple bond linkage. This polarization is caused by the differences in electronegativity among the atoms in the cumulene

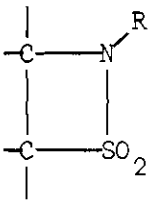


system. Another factor to consider in assessing reactivity in cycloaddition reactions is the transition state stability, which is also dependent on electronegativity. Theoretically then one might predict that N-sulfonylamines would possess intermediate reactivity between



sulfenes (least reactive) and sulfur trioxide (most reactive).

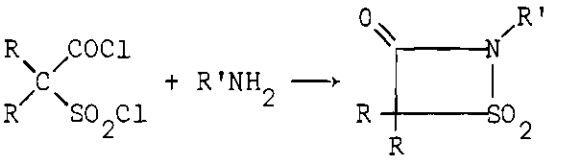
The product which would result from cycloaddition of an N-sulfonylamine to a carbon-carbon π-bond is the 1,2-thiazetidine-1, 1-dioxide, IX. Such structures are rare, and although a few compounds



IX

containing structure IX have been reported, most of the structural assignments for these compounds appear to have been ambiguous (6).

One apparently reliable and well-investigated synthesis involves the reaction of an α,α-dialkyl-α-chlorosulfonylacetyl chloride (X) with primary amines or ammonia to give a 4,4-dialkyl-1,2-thiazetidine-3-one-1,1-dioxide (XI, R' = alkyl or H) (7,8).



X XI

However, this synthesis is restricted to the preparation of mixed imides which are disubstituted at the 4-position.

It was apparent from the literature cited that no general synthesis of N-sulfonylamines had been developed. In addition, the paucity of techniques for preparing 1,2-thiazetidine-1,1-dioxides (IX) indicated that the utilization of N-sulfonylamines in cycloaddition reactions would be valuable for the synthesis of such heterocycles.

The purpose of this research was to develop a general route to

N-sulfonylamines and to investigate their synthetic applications, especially with regard to use in cycloaddition reactions.

CHAPTER II

EXPERIMENTAL

Apparatus and Techniques

Before use anhydrous benzene was distilled from sodium and stored over sodium ribbon. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride within 24 hours before use. Triethylamine was distilled and stored over potassium hydroxide pellets. Acetonitrile was dried by distillation from powdered phosphorus pentoxide. Chloroform and n-hexane were distilled and the first portions of the distillates were discarded.

Melting points were determined using a Fisher-Johns hot stage melting point apparatus and are uncorrected. Elemental microanalyses were performed by Huffman Laboratories, Wheatridge, Colorado. Infrared spectra were obtained using either a Perkin-Elmer, Model 137, or a Perkin-Elmer, Model 457, recording spectrophotometer. Sodium chloride solvent cells (0.2 mm) were used for determining solution infrared spectra. Potassium bromide was used in preparing samples in pellets. The listings of infrared absorptions include those which are relevant to structural arguments and other strong absorptions.

Nuclear magnetic resonance spectra were obtained using a Varian, Model A-60, spectrometer. Tetramethylsilane (TMS) was used as an internal standard except for samples dissolved in deuterium oxide or benzene. For samples dissolved in benzene, calibration was accomplished

using the benzene protons (τ 2.63). Chemical shifts are reported in units of τ ($\tau = 10 - \delta$). The abbreviations, s, d, t, q and m, refer to singlet, doublet, triplet, quartet and multiplet, respectively. For a multiplet a single value for the chemical shift is given which is the center of gravity of the multiplet. In the case of multiplets for which the center of gravity is not easily discerned and for unresolved mixtures of multiplets, the chemical shifts are reported as a range.

Mass spectral data were obtained using either a LKB, Model 9000, gas chromatograph—single focusing mass spectrometer (using a modified inlet system) or a Varian, Model M66, mass spectrometer.*

Gas-liquid phase chromatography was performed using an F and M, Model 700, dual column gas chromatograph fitted with a silicone rubber column (four feet) and using helium as the carrier gas. Solid-liquid phase chromatography was accomplished using silica gel (Curtin, 60-200 mesh), alumina (Fisher, 80-200 mesh) or florisil (Fisher, 60-100 mesh) as indicated. Thin layer chromatography was performed using silica gel G (according to Stahl; E. Merck AG, Darmstadt) on 3" X 1" microscope slides. In each case the liquid phase is indicated.

In several examples a sulfamoyl chloride was added to a solution of triethylamine and other reactants. In each case the apparatus used consisted of a cylindrical chamber topped with a head fitted with an addition funnel and inlet and outlet ports for replacing air in the

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*The author is indebted to Mr. G. Turner for the measurements using the Varian spectrometer.

system with dry nitrogen. Both the head and the addition funnel were fitted with septum caps for injecting solutions into the system. In all cases where triethylamine hydrochloride was precipitated, its identity was confirmed by melting point and comparison of infrared spectra with an authentic sample. Unless otherwise indicated, yields of triethylamine hydrochloride were approximately quantitative.

The form used in reporting physical data of compounds follows that recommended for American Chemical Society journals (9).

N-Sulfonylethylamine

N-Sulfonylethylamine (XII)

Ethylsulfamoyl chloride (10) (3.85 g, 0.0268 mole) in 10 ml of toluene was added dropwise under nitrogen over a five-minute period to a solution of 8 ml of triethylamine in 35 ml toluene at -78°C. The solution was stirred at -78°C for 30 min and then filtered at this temperature into a flask containing 5 ml of aniline. The precipitate of triethylamine hydrochloride, after washing with several portions of benzene and drying under reduced pressure, weighed 3.6 g (98.5 per cent). A portion of ether (250 ml) was added to the above filtrate and this solution was extracted with three 50 ml portions of 6M hydrochloric acid. The ether layer was washed with 25 ml of water and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a yellow oil which was chromatographed over 40 g alumina. The fraction obtained using 1:1 (v/v) ether-chloroform as an eluent gave 1.098 g (20.5 per cent) of a colorless oil which solidified on cooling. Recrystallization from benzene-

hexane gave colorless crystals of N-ethyl-N'-phenylsulfamide (XIII): mp 72-72.5°C; ir ($CHCl_3$) 3320 (N-H), 2990, 1605, 1495, 1355 and 1155 cm^{-1} (SO_2-N); nmr ($CDCl_3$) τ 2.25 (s, 1H), 2.70-3.20 (m, 5H), 4.51 (broad, t, 1H, $\underline{J}$ = 6 Hz), 7.05 (m, 2H) and 9.07 (t, 3H, $\underline{J}$ = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 200 (100).

Compound XIII was also prepared by reacting ethylsulfamoyl chloride and aniline directly.

In another example, the same procedure was used except that after addition of the ethylsulfamoyl chloride the mixture was stirred at -78°C for only 15 min before filtering. In this case 54 per cent of XIII was isolated as previously described, but only 92 per cent of the theoretical amount of triethylamine hydrochloride was collected.

In yet another example, the aniline was omitted in the receiving flask during filtration. As the filtrate which contained N-sulfonylethylamine (XII) was allowed to warm to room temperature, an exothermic polymerization occurred. Evaporation of the solvent yielded a light yellow oil which could be precipitated from a chilled ethanol solution. Filtration gave a polymer (XIV) in the form of a white powder having no definitive melting point but which began to soften at 110°C.

Reaction with Ketene Diethylacetal

Ethylsulfamoyl chloride (7.0 g, 0.0487 mole) in 5 ml of benzene was added dropwise under nitrogen to a stirred solution of 6.1 g (0.0725 mole) of ketene diethylacetal (11) and 7.0 ml of triethylamine in 20 ml of benzene at 5°C. The addition was accomplished over a two-hour period after which the mixture was filtered to remove the precipitated triethylamine hydrochloride. Evaporation of the solvent under

reduced pressure afforded a residual oil which was distilled in a molecular still at 60°C (pot temperature) and 1 X 10^{-3} mm. The distillate was a colorless oil, and tlc ($CHCl_3$) indicated it to be a mixture of two components, XV and XVI.

A portion of the distillate (1.50 g) was dissolved in 100 ml of 95 per cent ethyl alcohol which had been acidified with 0.1 ml of concentrated hydrochloric acid, and this solution was allowed to stand for 12 hr. The solvent was then removed under reduced pressure, and the residual oil was dissolved in 100 ml of ether. The ether solution was washed with 50 ml of ice cold water. The solvent was then evaporated under reduced pressure leaving a colorless oil (900 mg) which tlc ($CHCl_3$) indicated to be pure ethyl (ethylsulfamoyl)acetate (XVI): ir (liquid film) 3325 (N-H), 3000, 1740 (C = O), 1330 and 1160 cm^{-1} (SO_2-N); nmr ($CDCl_3$) τ 4.52 (broad, t, 1H, J = 6 Hz), 5.85 (q, 2H, J = 7 Hz), 6.02 (s, 2H), 6.92 (m, 2H), 8.82 (t, 3H, J = 7 Hz) and 8.92 (t, 3H, J = 7 Hz).

The nmr resonance of XVI was subtracted from that of the distillate (mixture of XV and XVI) to give the nmr spectrum of XV alone: nmr (CCl_4) τ 6.40 (q, 4H, J = 7 Hz), 6.87 (m, 2H*), 7.90 (s, 1H), 8.68 (t, 3H,* J = 7 Hz) and 8.83 (t, 6H,* J = 7 Hz).

Compound XVI (900 mg) was dissolved in 100 ml of 1 per cent sodium hydroxide solution and stirred at ambient temperatures for 18 hours. The resulting solution was acidified with dilute hydrochloric acid and extracted with three 100 ml portions of ether. The ether

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*Estimated.

extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left a colorless oil which crystallized from chloroform yielding 325 mg of colorless needles of (ethylsulfamoyl)acetic acid (XVII): mp 120°C; ir ($CHCl_3$) 3300 (N-H), 2950, 2595 and 2510 (weak), 1720 (C = O), 1325 and 1155 cm^{-1} (SO_2-N); nmr (98 per cent D_2O, calibrated using external TMS) τ 5.71 (s, 2H), 6.79 (q, 2H, J = 7 Hz) and 8.80 (t, 3H, J = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 166 (1.4), 152 (71), 150 (10).

Preparation of (Ethylsulfamoyl)acetic Acid (XVII)

Starting with sulfoacetic acid monohydrate, chlorosulfonylacetic acid was synthesized by a procedure described previously (12). Chlorosulfonylacetic acid (234 mg) was dissolved in 30 ml of benzene, and to this solution was added dropwise 3 ml of anhydrous ethylamine in 25 ml of benzene. After standing at ambient temperatures for several hours, the benzene solution was treated with 200 ml of dilute hydrochloric acid. This mixture was extracted with four 100 ml portions of ether, and the combined ether extracts were dried using anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure left colorless crystals which after recrystallization from chloroform afforded colorless needles of (ethylsulfamoyl)acetic acid (XVII): mp 120°C. Mixed melting point and infrared spectra comparisons indicated that XVII prepared by this method was identical to that derived from the reaction of N-sulfonylethylamine (XII) with ketene diethylacetal.

Reaction with 2-(Dichloromethylene)-1,3-dioxolane

Ethylsulfamoyl chloride (6.46 g, 0.0450 mole) in 10 ml of benzene was added dropwise under nitrogen over a two-hour period to a stirred

solution containing 7.20 g (0.0465 mole) of 2-(dichloromethylene)-1,3-dioxolane (13) and 8.6 ml of triethylamine in 25 ml of benzene at ambient temperatures. After the addition the mixture was stirred overnight at ambient temperatures. The precipitate of triethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure leaving a residual dark red-brown oil. Removal of the last traces of solvent at 0.1 mm pressure caused the oil to solidify. Recrystallization from carbon tetrachloride gave 10.1 g (85.6 per cent) of crude 4,4-dichloro-3,3-ethylenedioxy-2-ethyl-1,2-thiazetidine-1,1-dioxide (XVIII) as off-white plates. Another recrystallization from carbon tetrachloride solution after decoloration with charcoal gave XVIII as colorless plates: mp 74-75°C; ir ($CHCl_3$) 2995, 1460, 1340, 1170, 1135 and 890 cm^{-1}; nmr ($CDCl_3$) τ 5.73 (m, 4H), 6.72 (q, 2H, $\underline{J}$ = 7 Hz) and 8.67 (t, 3H, $\underline{J}$ = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 262 (5), 154 (46), 107 (42).

The ions in the mass spectrum at m/e 262 and m/e 154 had accompanying $(M+2)^+$ and $(M+4)^+$ signals in proportions corresponding to the isotopic combinations of two chlorine atoms (14).

Anal. Calcd for $C_6H_9Cl_2NO_4S$: C, 27.49; H, 3.47; N, 5.34; S, 12.23. Found: C, 27.62; H, 3.53; N, 5.41; S, 11.98.

Reaction with Isobutyraldehyde Pyrrolidine Enamine

Ethylsulfamoyl chloride (3.44 g, 0.0240 mole) in 10 ml of benzene was added dropwise under nitrogen over 40 minutes to a solution of 3.285 g (0.0285 mole) of the pyrrolidine enamine of isobutyraldehyde (15) and 4.0 ml of triethylamine in 20 ml of benzene at ambient temperatures. The mixture was stirred for an additional 30 min after which

time the precipitate of triethylamine hydrochloride was removed by filtration and the solvent was evaporated from the filtrate under reduced pressure. After the last traces of solvent were removed at 0.1 mm pressure, the residual red, oily, impure 4,4-dimethyl-2-ethyl-3-(N-pyrrolidino)-1,2-thiazetidine-1,1-dioxide (XIX) displayed the following nmr spectrum: (benzene) τ 6.34 (s, 1H), 6.78 (q, 2H, $\underline{J}$ = 7 Hz), 7.00-7.49 (m, 4H), 8.06-8.38 (m, 4H), 8.43 (s, 6H) and 8.72 (t, 3H, $\underline{J}$ = 7 Hz).

After attempts to crystallize XIX were unsuccessful, the oil was chromatographed over florisil (40 g). Elution with benzene gave α-(ethylsulfamoyl)isobutyraldehyde (XX) as a yellow oil (2.99 g) which was judged to be pure by tlc (benzene). The spectral data for XX are: ir (liquid film) 3340 (N-H), 3000, 2890 and 2750 (weak), 1740 (C = O), 1450, 1335 and 1170 cm^{-1} (SO_2-N); nmr (benzene) τ 0.24 (s, 1H), 6.82 (q, 2H, $\underline{J}$ = 7 Hz), 8.48 (s, 6H) and 8.83 (t, 3H, $\underline{J}$ = 7 Hz).

Treatment of XX with an ethanolic solution of 2,4-dinitrophenylhydrazine and sulfuric acid (16) gave, after recrystallization from ethyl acetate, bright yellow needles of the 2,4-dinitrophenylhydrazone (XXI): mp 186.5-87.5°C; ir (nujol mull) 1625 cm^{-1} (C = N).

Anal. Calcd for $C_{12}H_{17}N_5O_6S$: C, 40.10; H, 4.78; N, 19.49; S, 8.92. Found: C, 40.82; H, 4.92; N, 19.03; S, 8.46.

In another example, XIX was prepared exactly as before. The red oil (XIX) was dissolved in 30 ml of benzene, and to this solution was added dropwise 8.5 g of methyl iodide in 10 ml of benzene. After one hour a red oil began to separate from the solution. The mixture was left standing overnight, and by the next day a red-brown crystalline

precipitate had deposited from the benzene solution. The solvent was removed by decantation, and the last traces of the solvent were removed at 0.1 mm. Under vacuum the crystals, an impure sample of the methiodide salt (XXII) of XIX, deliquesced to a viscous red-brown oil. Compound XXII displayed the following nmr spectrum: (DMSO-d_6) τ 6.25-7.30 (broad, m, 6H), 6.38 (s, 1H*), 6.74 (s, 3H*), 7.69-8.28 (m, 4H), 8.57 (s, 6H) and 8.91 (t, 3H, J = 7 Hz).

Attempts to purify XXII by recrystallization were unsuccessful.

Reaction with N,N-Dimethylaniline

Ethylsulfamoyl chloride (3.06 g, 0.0213 mole) in 10 ml of benzene was added dropwise under nitrogen to a stirring solution containing 2.58 g (0.0213 mole) of N,N-dimethylaniline at ambient temperatures. After addition was complete, 150 ml of water was added to the benzene solution, and the aqueous layer was acidified with concentrated hydrochloric acid. The mixture was extracted with five 50 ml portions of ether. The combined ether extracts were washed with 50 ml of water and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure gave 2.30 g (47.4 per cent) of N,N-dimethyl-N'-ethylsulfanilamide (XXIII) as off-white needles. An analytical sample was obtained by repeated recrystallization from a chloroform-hexane solution and had: mp 160-62°C; ir ($CHCl_3$) 3355 (N-H), 2970, 1600, 1505, 1370, 1315 and 1150 cm^{-1}; nmr (DMSO-d_6) τ 2.75 (m, 4H), 6.37 (broad, s, 1H), 6.99 (s, 6H), 7.41 (q, 2H, J = 7 Hz) and 8.99 (t, 3H, J = 7 Hz).

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*Assumed.

Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.60; H, 7.08; N, 12.27; S, 14.07. Found: C, 52.43; H, 6.95; N, 12.36; S, 14.12.

N-Sulfonylbenzamide

N-Sulfonylbenzamide (XXIV)

Benzoylsulfamoyl chloride (17) (1.00 g, 0.00456 mole) in 10 ml of THF was added dropwise under nitrogen over a 10-min period to a solution of 5 ml of triethylamine in 20 ml of THF at -78°C. The mixture was stirred at -78°C for eight hours and then filtered at that temperature into a flask containing 5 ml of anhydrous ethylamine. The precipitate of triethylamine hydrochloride weighed 605 mg (96 per cent). Evaporation of the solvent from the filtrate gave a light yellow oil which was chromatographed over silica gel (10 g). Elution with chloroform and recrystallization from chloroform-hexane gave colorless needles (685 mg, 66 per cent) of N-benzoyl-N'-ethylsulfamide (XXV): mp 158-59°C; ir ($CHCl_3$) 3400 (N-H), 3000, 1700 (C = O), 1605, 1455, 1360 and 1160 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.31; N, 12.27; S, 14.04. Found: C, 47.12; H, 5.31; N, 12.12; S, 14.12.

Compound XXV was also prepared by reacting benzoylsulfamoyl chloride and anhydrous ethylamine directly.

In another example, the ethylamine was omitted in the receiving flask during filtration. The filtrate was allowed to warm to 30°C and stand at that temperature for several hours. Evaporation of solvent at reduced pressure gave a colorless liquid having an infrared spectrum identical to that of an authentic sample of phenyl isocyanate.

Reaction with Ethyl Vinyl Ether in Excess Triethylamine

Benzoylsulfamoyl chloride (5.0 gm, 0.0228 mole) in 10 ml of DME was added dropwise under nitrogen over a two-hour period to a solution containing 3.58 g (0.0498 mole) of ethyl vinyl ether and 3.0 g (0.0297 mole) of triethylamine in 20 ml of benzene at ambient temperatures. After the addition, the mixture was stirred at ambient temperatures for 12 hr, and the precipitate of triethylamine hydrochloride was removed by filtration. The solvent was evaporated from the filtrate under reduced pressure to provide a dark yellow oil which was chromatographed over silica gel (70 g). Elution with benzene gave a light yellow oil (3.27 g) which was crystallized from benzene-hexane solution giving colorless needles of N-benzoyl-β-ethoxyvinylsulfonamide (XXVI): mp 135-36°C; ir ($CHCl_3$) 3290, 3095, 2990, 1710 (C = O), 1625 (C = C), 1610, 1450, 1340 and 1150 cm^{-1}; nmr ($CDCl_3$) τ 2.15-2.70 (m, 7H), 4.08 (d, 1H, J = 12 Hz), 6.11 (q, 2H, J = 7 Hz) and 8.73 (t, 3H, J = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 255 (0.24), 191 (1.4), 105 (82), 88 (100), 60 (40).

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.74; H, 5.14; N, 5.49; S, 12.56. Found: C, 51.69; H, 5.32; N, 5.51; S, 12.95.

Reaction with Ethyl Vinyl Ether in Limited Triethylamine

Triethylamine (0.462 g, 0.00456 mole) in 5 ml of benzene was added dropwise under nitrogen over a 25-min period to a solution containing 1.00 g (0.00456 mole) of benzoylsulfamoyl chloride and 2.6 g of ethyl vinyl ether in 20 ml of benzene-DME (1:1, v/v) at ambient temperatures. The mixture was stirred at ambient temperatures for 90 min after the addition was complete, and then the precipitate of

triethylamine hydrochloride was removed by filtration. Evaporation of the solvents under reduced pressure gave a brown solid residue. Recrystallization from benzene-hexane provided colorless needles (820 mg, 71 per cent) of 2-benzoyl-3-ethoxy-1,2-thiazetidine-1,1-dioxide (XXVII): mp 87-88°C; ir ($CHCl_3$) 2905, 1705 (C = O), 1450, 1350 and 1165 cm^{-1} (SO_2-N); nmr ($CDCl_3$) τ 1.80-2.70 (m, 5H), 4.07 (m, 1H), 5.62-6.80 (m, 2H), 5.85 (q, 2H, J = 7 Hz) and 8.62 (t, 3H, J = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 255 (0.8), 150 (0.5), 104 (100).

Decoupling* of the heterocyclic ring protons in the nmr revealed the theoretical 15 lines for the ABX system (18) with J_{AB} = -14 Hz, J_{AX} = 9 Hz and J_{BX} = 3 Hz (H_A *trans* to H_X).

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.74; H, 5.14; N, 5.49; S, 12.56. Found: C, 51.81, 51.87; H, 6.43, 6.32; N, 5.52; S, 12.55.

A small amount (approximately 5 mg) of colorless needles crystallized from the filtrate from the first recrystallization of XXVII. Although an insufficient amount was obtained for complete analysis, this material appeared to be an isomer of XXVII, 2,3-dihydro-2-ethoxy-6-phenyl-1,4,5-oxathiazine-4,4-dioxide (XXVIII): mp 130-32°C; ir ($CHCl_3$) 2985, 1605 (C = N), 1570, 1440, 1335, 1155 and 1105 cm^{-1}.

Conversion of XXVII to XXVI

Compound XXVII (30 mg) was dissolved in 10 ml of benzene containing 0.4 ml of triethylamine, and the solution was allowed to stand at ambient temperatures overnight. Evaporation of the solvent under reduced pressure gave a colorless oil which was chromatographed over

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*The author is indebted to Dr. J. R. Dyer and Mr. J. B. Dawson for these measurements.

silica gel (5 g). Elution with absolute ethanol gave colorless crystals (19 mg) which were identical to XXVI by mixed melting point and infrared spectra comparisons.

Reaction with N,N-Dimethylaniline

Benzoylsulfamoyl chloride (3.0 g, 0.0137 mole) in 10 ml of DME was added dropwise under nitrogen at ambient temperatures to a solution containing 3.31 g (0.0273 mole) of N,N-dimethylaniline in 20 ml of benzene. The solution was stirred for two hours at ambient temperatures and then poured into 150 ml of dilute aqueous hydrochloric acid. This mixture was extracted with four 75 ml portions of ether. The extracts were combined, washed with 30 ml of water, and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure gave a residue which was recrystallized from absolute ethanol providing 326 mg of off-white crystals. The nmr (DMSO-d_6) of this material showed, in addition to aromatic (τ 1.84-3.27) and nitrogen-bound protons (τ 5.57, broad), two singlets at τ 6.92 and 7.01 in an area ratio of approximately 4:6 indicating a mixture of ortho- (40 per cent, XXIX) and parasubstituted (60 per cent, XXX) products. Recrystallization from a dilute ethanol solution gave large colorless needles (35 mg) of N,N-dimethyl-N'-benzoylsulfanilamide (XXX): mp 158-59°C; ir (KBr) 3255 (N-H), 2920, 1685 (C = O), 1590, 1495, 1335, 1150 and 820 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.20; H, 5.31; N, 9.21; S, 10.53. Found: C, 59.25; H, 5.25; N, 9.09; S, 10.43.

(Carboxysulfamoyl)triethylammonium Hydroxide, Inner Salt, Ethyl Ester

(Carboxysulfamoyl)triethylammonium Hydroxide, Inner Salt, Ethyl Ester (XXXI)

Carbethoxysulfamoyl chloride (19) (3.75 g, 0.0200 mole) in 10 ml of benzene was added dropwise under nitrogen over a 30 min period to a solution containing 5.0 g (0.0495 mole) of triethylamine in 25 ml of benzene at ambient temperatures. After the addition was complete, the precipitate of triethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure giving a colorless oil which solidified on standing. Recrystallization from benzene solution gave colorless crystals (4.10 g, 81 per cent) of (carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester (XXXI): mp 66-69°C; ir ($CHCl_3$) 2990, 1685 (C = O), 1460, 1260 and 1105 cm^{-1}; nmr (benzene) τ 5.71 (q, 2H, J = 7 Hz), 6.71 (q, 6H, J = 7 Hz), 8.72 (t, 3H, J = 7 Hz) and 8.85 (t, 9H, J = 7 Hz).

Anal. Calcd for $C_9H_{20}N_2O_4$: C, 42.82; H, 8.00; N, 11.10; S, 12.70. Found: C, 42.74; H, 7.85; N, 11.11; S, 12.71.

Monohydrate of XXXI (XXXII)

When XXXI was dissolved in benzene containing 1 per cent water and allowed to stand for several hours at ambient temperatures, a crystalline precipitate formed which upon filtration gave the monohydrate of XXXI (XXXII) as transparent plates: mp 89-90°C; ir ($CHCl_3$) 3410, 2980, 1720 (C = O), 1465, 1435, 1270 and 1035 cm^{-1}; nmr ($CDCl_3$) τ 1.62 (broad, s, 2H), 5.86 (q, 2H, J = 7 Hz), 6.70 (q, 6H, J = 7 Hz), 8.63 (t, 9H, J = 7 Hz) and 8.77 (t, 3H, J = 7 Hz).

It was possible to convert XXXII to XXXI by gentle heating under vacuum. In one example, XXXI was dissolved in water and allowed to stand for several hours at 25°C. Evaporation of the water under reduced pressure at 45-50°C gave XXXI displaying the same melting point and infrared spectrum as before hydration.

Reaction with Aniline

Compound XXXI (2.00 g, 0.00792 mole) was dissolved in 10 ml of benzene. Upon addition of 2 ml of aniline, an exothermic reaction occurred. The benzene solution was added to 100 ml of dilute hydrochloric acid, and this mixture was extracted with four 75 ml portions of ether. The combined ether extracts were washed with 50 ml of water and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure, followed by recrystallization of the residue from a benzene solution, gave 1.77 g (92 per cent) of colorless needles of N-carbethoxy-N'-phenylsulfamide (XXXIII): mp 140-41°C [lit. (20) mp 140-41°C]; ir ($CHCl_3$) 3380 (N-H), 3000, 1745 (C = O), 1600, 1475, 1430, 1350 and 1160 cm^{-1}; nmr (acetone) τ 0.94 (broad, s, 1H), 2.50-2.79 (m, 5H), 5.78 (q, 2H, J = 7 Hz), 6.77 (s, 1H) and 8.77 (t, 3H, J = 7 Hz).

Reaction with Isopropyl Alcohol

Compound XXXI (1.0 g) was dissolved in 10 ml of isopropyl alcohol containing 3 ml of benzene and then allowed to stand overnight at ambient temperatures. Evaporation of the solvents under reduced pressure gave a colorless oil which was dissolved in 60 ml of dilute hydrochloric acid and extracted with four 50 ml portions of ether. After the ether extracts were dried over anhydrous magnesium sulfate, the ether was evaporated giving isopropyl carbethoxysulfamate (XXXIV) as a colorless

oil: ir ($CHCl_3$) 3400 (N-H), 2990, 1755 (C = O), 1465, 1435, 1370 and 1165 cm^{-1}; nmr ($CDCl_3$) τ 1.28 (s, 1H), 4.95 (m, 1H), 5.72 (q, 2H, $\underline{J}$ = 7 Hz), 8.59 (d, 6H, $\underline{J}$ = 6 Hz) and 8.70 (t, 3H, $\underline{J}$ = 7 Hz).

Compound XXXIV was also prepared by reacting carbethoxysulfamoyl chloride and isopropyl alcohol directly.

When XXXIV dissolved in acetone was injected into the gas-liquid chromatograph (injector temperature 230°C, CT 120°C, HFR 40 cc/min), the chromatogram showed four peaks with retention times of 0.90, 1.00, 1.25 and 5.70 min. The peak with RT 1.25 min was determined to be acetone by comparison of retention times with an authentic sample and by enrichment of the mixture. The vapors from the peaks preceding the acetone could not be condensed in a collection tube immersed in a dry ice acetone bath However, the vapors with retention time 5.70 min were collected in this manner giving a colorless crystalline compound which was shown to be ethyl carbamate by comparison of GLC retention times and infrared spectra with an authentic sample.

In another example, XXXIV was placed in a micro Hickmann still and heated at 0.1 mm. The oil began to decompose at 60°C and decomposed rapidly at 90°C, giving once again ethyl carbamate.

Reaction with 1-Vinyl-2-pyrrolidinone

Compound XXXI (0.9171 g, 0.00363 mole) and 1-vinyl-2-pyrrolidinone (0.462 g, 0.00408 mole) were dissolved in 10 ml of acetonitrile and allowed to stand in a flask fitted with a calcium chloride drying tube for 13 hr at 30°C. At the end of that time, tlc ($CHCl_3$) indicated little or no reaction. The flask was then fitted with a reflux condenser and the solution was heated at 50°C for 18 hr. At the end of

this time, tlc ($CHCl_3$) indicated the disappearance of XXXI and only a small amount of residual 1-vinyl-2-pyrrolidinone in comparison to a new polar compound. The solvent was evaporated under reduced pressure yielding a clear red oil which was then dissolved in 50 ml of dilute hydrochloric acid. The acid solution was extracted with three 40 ml portions of chloroform, and the combined chloroform extracts were dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave, after recrystallization from chloroform-hexane, colorless needles (478 mg, 50.3 per cent) of N-carbethoxy-β-(1-pyrrolidine-2-one)vinylsulfonamide (XXXV): mp 149-51°C; ir ($CHCl_3$) 3450 (N-H), 1750 (C = O), 1635 (C = C), 1390, 1340 and 1140 cm^{-1}; nmr ($CDCl_3$) τ 1.89 (d, 1H, J = 14 Hz), 4.02 (d, 1H, J = 14 Hz), 5.74 (q, 2H, J = 7 Hz), 6.39 (t, 2H, J = 7 Hz), 7.40-7.89 (m, 4H) and 8.71 (t, 3H, J = 7 Hz).

Anal. Calcd for $C_9H_{14}N_2O_5S$: C, 41.21; H, 5.39; N, 10.68; S, 12.22. Found: C, 40.88; H, 5.41; N, 10.45; S, 12.10.

Reaction with N,N-Dimethylaniline

Compound XXXI (335 mg) was dissolved in 10 ml of benzene containing 1.0 ml of N,N-dimethylaniline and allowed to stand at ambient temperatures overnight during which time a colorless precipitate was deposited from the benzene solution. To this mixture was added 30 ml of water, and it was then acidified with concentrated hydrochloric acid. This mixture was then extracted with three 25 ml portions of ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure gave colorless needles (130 mg, 36 per cent) of N,N-dimethyl-N'-carbethoxysulfanilamide (XXXVI). An analytical sample of XXXVI was prepared by

recrystallization from chloroform-benzene: mp 184-90°C [lit. (21) mp 192-94°C]; ir ($CHCl_3$) 3390 (N-H), 3010, 1740 (C = O), 1600, 1470, 1340 and 1150 cm^{-1}; nmr (DMSO-d_6) τ 2.90 (m, 4H), 6.05 (q, 2H, $\underline{J}$ = 7 Hz), 6.46 (broad, s, 1H), 7.07 (s, 6H) and 8.90 (t, 3H, $\underline{J}$ = 7 Hz).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.93; N, 10.29; S, 11.77. Found: C, 48.24; H, 5.85; N, 10.33; S, 11.56.

In another example, 5.0 g (0.0266 mole) of carbethoxysulfamoyl chloride in 10 ml of benzene was added dropwise under nitrogen over a one-hour period at ambient temperatures to a solution of 6.45 g (0.0580 mole) of N,N-dimethylaniline in 15 ml of benzene. The solution was stirred at ambient temperatures for two hours after the addition was completed and was then poured into 300 ml of dilute hydrochloric acid. This mixture was extracted with five 100 ml portions of ether. The combined ether extracts were washed with 30 ml of water and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure gave 4.38 g (60.7 per cent) of XXXVI.

Reaction with Tetramethylallene

Compound XXXI (0.50 g, 0.00198 mole) and tetramethylallene (0.38 g, 0.00396 mole) were dissolved in 3 ml of acetonitrile in a flask fitted with a reflux condenser and a calcium chloride drying tube. The solution was heated at 60°C for three hours. Evaporation of solvent under reduced pressure gave a red oil which was chromatographed over florisil (9 g). Elution with benzene-chloroform (1:1, v/v) gave 228 mg of colorless crystals which were shown by GLC to be a

mixture of two compounds, XXXVII (15 per cent*) and XXXVIII (85 per cent*). The major component of the mixture was purified by repeated recrystallization from benzene-hexane solution providing colorless needles of 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine-4,4-dioxide (XXXVIII): mp 81-83°C; ir ($CHCl_3$) 2985, 1615 (C = N), 1460, 1330 and 1130 cm^{-1}; nmr ($CDCl_3$) τ 5.60 (q, 2H, $\underline{J}$ = 7 Hz), 7.65 (s, 3H), 7.96 (s, 3H), 8.19 (s, 6H) and 8.62 (t, 3H, $\underline{J}$ = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 247 (2), 232 (57), 202 (4), 160 (100).

Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.60; H, 6.89, N, 5.67; S, 12.95. Found: C, 48.54; H, 6.91; N, 5.72; S, 13.07.

Compounds XXXVII and XXXVIII could also be separated by GLC (CT 200°C, HFR 120 cc/min). The mixture was separated in this way giving 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidine-1,1-dioxide (XXXVII) as colorless needles (RT 1.90 min**): mp 150-51°C; ir ($CHCl_3$) 2980, 1725 (C = 0), 1695 (C = C), 1440, 1370, 1315 and 1160 cm^{-1}; nmr ($CDCl_3$) τ 5.58 (q, 2H, $\underline{J}$ = 7 Hz), 7.90 (s, 3H), 8.09 (s, 3H), 8.24 (s, 6H) and 8.65 (t, 3H, $\underline{J}$ = 7 Hz); mass spectrum (70 eV) m/e (relative intensity) 247 (0.5), 232 (100), 202 (5), 176 (2), 160 (100).

The molecular formula of XXXVII was confirmed by exact mass determinations. Calcd for $C_{10}H_{17}NO_4S$ $(M)^+$: 247.088. Found: 247.086. Calcd for $C_9H_{14}NO_4S$ $(M-15)^+$: 232.064. Found: 232.062.

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*Based on GLC and nmr spectrum of the mixture.

**Compound XXXVIII had a GLC retention time of 3.65 min.

Attempted Reaction with Allene

A bomb with a capacity of 250 ml was charged with a solution of 7.40 g of XXXI in 40 ml of acetonitrile. After the bomb was cooled to -78°C and evacuated to 25 mm, 10 g of allene were passed into the bomb which was then rocked for six hours at 65-70°C. After cooling and venting the bomb, the contents, a clear red solution, were removed. Evaporation of solvent under reduced pressure gave a red solid residue which was shown by infrared and nmr spectra and by tlc to be only slightly contaminated XXXI. The nmr spectrum showed no absorptions for protons resulting from the incorporation of allene.

Reaction with Hexamethylbicyclo[2.2.0]hexa-2,5-diene

Compound XXXI (1.206 g, 0.00458 mole) and 3.0 g of hexamethylbicyclo[2.2.0]hexa-2,5-diene* were dissolved in 4 ml of acetonitrile-benzene (1:1, v/v) and heated at 60°C for three hours in a flask fitted with a reflux condenser and calcium chloride drying tube. Cooling and evaporation of solvents under reduced pressure gave a residue composed of two separated oils. The lower layer was a dark red viscous oil while the upper layer was colorless. On standing at 0.1 mm pressure, the colorless oil crystallized. A portion (700 mg) of these colorless crystals was removed from the flask manually with a spatula. Recrystallization from benzene-hexane gave colorless crystals of an adduct (XXXIX): mp 140-41.5°C; ir ($CHCl_3$) 2980, 1730 (C = O), 1440, 1325, 1300 and 1145 cm^{-1}; nmr ($CDCl_3$) τ 5.64 (q, 2H, $\underline{J}$ = 7 Hz), 8.27 (s, 6H),

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*Purchased from Chemische Werke Huls AG, 4370 Marl (West Germany).

8.51 (s, 3H), 8.60 (t, 3H, J = 7 Hz), 8.72 (s, 3H) and 8.75 (s, 6H); nmr (benzene) τ 5.68 (q, 2H, J = 7 Hz), 8.34 (s, 3H), 8.49 (s, 6H), 8.70 (t, 3H, J = 7 Hz), 8.73 (s, 6H) and 8.75 (s, 3H); mass spectrum (70 eV) m/e (relative intensity) 313 (0.2), 268 (3), 149 (89).

Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.41; N, 4.47; S, 10.23. Found: C, 57.24; H, 7.54; N, 4.25; S, 10.00.

CHAPTER III

DISCUSSION OF RESULTS

The purpose of this research was to develop a general synthesis of N-sulfonylamines and to study their synthetic utility. As discussed in Chapter I, the intermediacy of N-sulfonylamines had been inferred from the examination of the structures of the products of certain reactions. However, no N-sulfonylamines had been isolated, and the only reported direct attempt to prepare this heterocumulene failed.

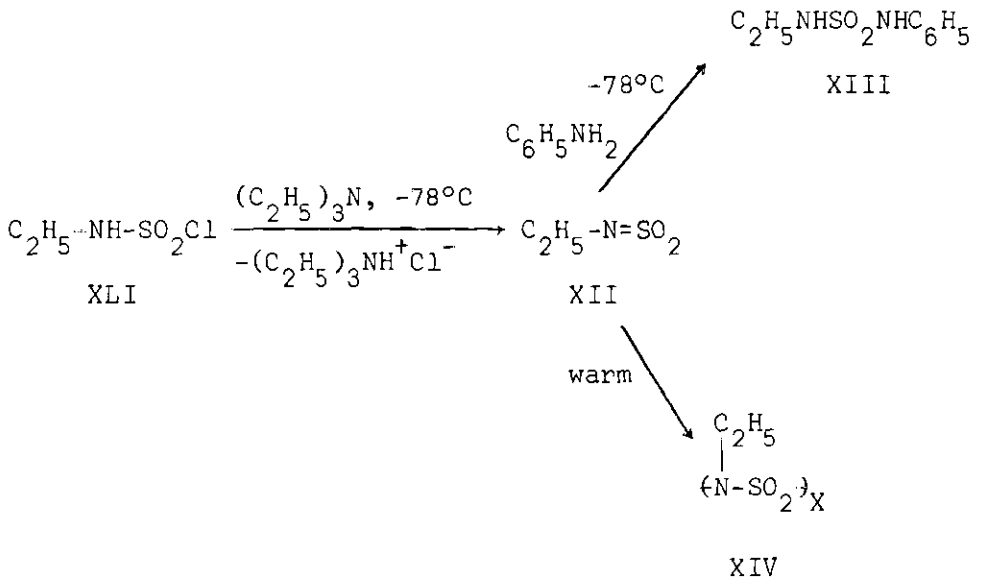
One approach to the N-sulfonylamine system which appeared attractive involved the reaction of a sulfamoyl chloride (XL) with a tertiary amine to give an N-sulfonylamine (I) and a tertiary amine

$$\underset{\text{XL}}{R\text{-}NH\text{-}SO_2Cl} + R'_3N \longrightarrow \underset{\text{I}}{R\text{-}N{=}S^{+}{=}O \;(O^-)} + R'_3NH^{+}Cl^{-}$$

hydrochloride. Such a scheme has precedence in the preparation of other heterocumulenes. Ketenes are quite simply prepared by the dehydrohalogenation of acyl halides with base (22). However, the excess base present during the reaction often catalyzes dimerization or polymerizations of the ketene, and therefore in many instances this method has been supplanted by other procedures (23). Sulfenes were first prepared by the dehydrohalogenation of sulfonyl chlorides possessing an

α-hydrogen substituent (24), and this method continues to be the one of choice for generating sulfenes *in situ* (25).

A simple procedure has been reported for preparing monoalkylsulfamoyl chlorides by refluxing primary amine hydrochlorides in sulfuryl chloride (10). Ethylsulfamoyl chloride (XLI) was prepared in this manner. When XLI was added to a toluene solution containing triethylamine at -78°C, a quantitative yield of triethylamine hydrochloride precipitated and was removed by filtration. When the filtrate containing N-sulfonylethylamine (XII) at -78°C was treated with aniline, N-ethyl-N'-phenylsulfamide (XIII) was the product. However, if the



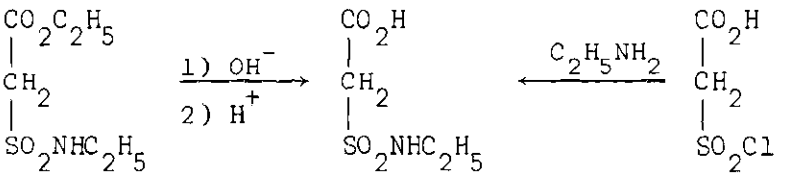
solution of XII was allowed to warm to room temperature, a polymerization occurred giving a white powdery polymer which probably possesses the linear structure XIV.

It was apparent that in order to pursue the chemistry of XII

reactions must either be carried out at low temperatures or XII must be generated in the presence of trapping agents. The latter method was generally found to be more desirable in order to delineate the reactions of this new functional group.

Compound XII, in its inability to be isolated from solution, demonstrated a high reactivity which is also characteristic of sulfenes. And like sulfenes (26), N-sulfonylamines were predicted to behave as electrophilic π-systems. Accordingly, studies designed to investigate the ability of N-sulfonylamines to participate in thermal cycloaddition reactions centered on reactions with electron-rich olefins.

When XII was generated *in situ* in a solution containing ketene diethylacetal (11), a mixture of two products was obtained. One component of the mixture was shown to be ethyl (ethylsulfamoyl)acetate (XVI). The structure of XVI was confirmed by its hydrolysis to a



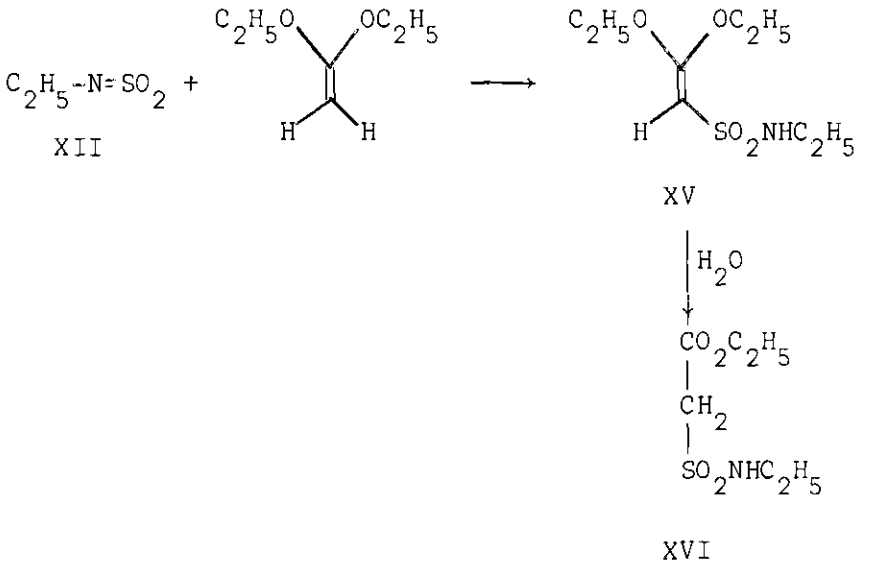
XVI XVII

product shown to be (ethylsulfamoyl)acetic acid (XVII). Compound XVII was synthesized independently by reacting chlorosulfonylacetic acid with ethylamine.

The other component of the mixture was determined to be (ethylsulfamoyl)ketene diethylacetal (XV) based on an nmr spectrum analysis

and the facile hydrolysis of XV to XVI. The nmr spectrum of XV showed, in addition to two O-ethyl groups [quartet (4H) at τ 6.40 and triplet (6H) at τ 8.83] and one N-ethyl group [multiplet (2H) at τ 6.87 and triplet (3H) at τ 8.68], a single olefinic proton singlet at τ 7.90.*

Compound XVI apparently was produced in the reaction through hydrolysis of XV during work-up.



The Woodward-Hoffman selection rules** based on orbital symmetry arguments forbid a concerted 2 + 2 cycloaddition (27,28). Therefore, it is suggested that the reaction of XII with ketene diethylacetal proceeds by way of the intermediate XLII. A base-assisted protonation and deprotonation of this intermediate would lead to the acyclic

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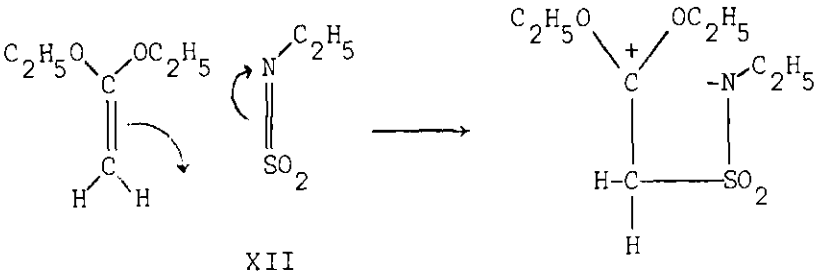
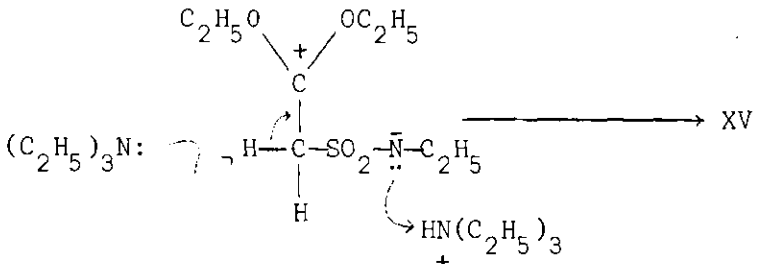
*The olefinic protons of ketene diethylacetal appear as a singlet resonating at τ 6.94.

**The Woodward-Hoffman rules are considered here only qualitatively since orbital symmetry arguments have not been rigorously applied to heterocyclic systems.



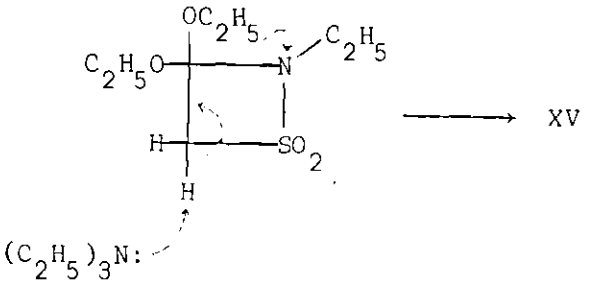
XII XLII

product (XV) of this reaction.



XLII

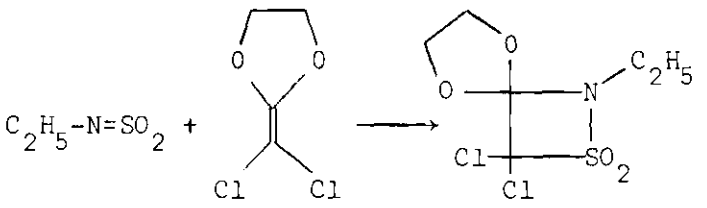
As an alternate route, XV may arise through the base-catalyzed ring-opening of the cyclic structure XLIII which results from ring-closure of XLII.



XLIII

Both of these routes to XV depend on the presence of the olefinic protons on the ketene diethylacetal. Therefore, it was determined to react XII with a ketene acetal which would give rise to a 1,2-thiazetidine-1,1-dioxide having no hydrogens at the 4-position. When N-sulfonylethylamine (XII) was generated in the presence of 2-(dichloromethylene)-1,3-dioxolane (13), 4,4-dichloro-3,3-ethylenedioxy-2-ethyl-

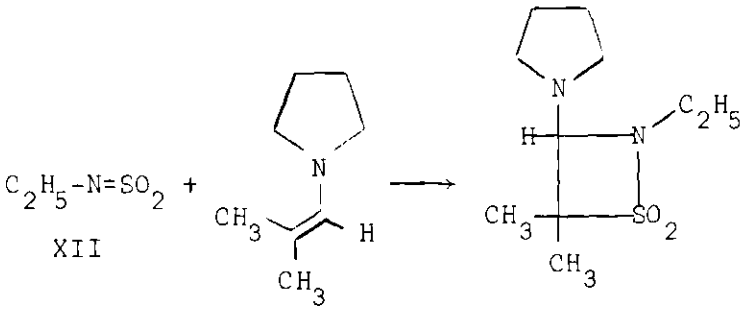
1,2-thiazetidine-1,1-dioxide (XVIII) was produced in good yield.



XII XVIII

The infrared and nmr spectra were consistent with the structure shown. The mass spectrum of XVIII displayed ions corresponding to cleavage of the ring system into its generators (m/e 154 and m/e 107) but none which would establish the orientation of the cycloaddition. Therefore, the orientation is based on the predicted polarization of XII* and on analogy to the reaction of XII with ketene diethylacetal.

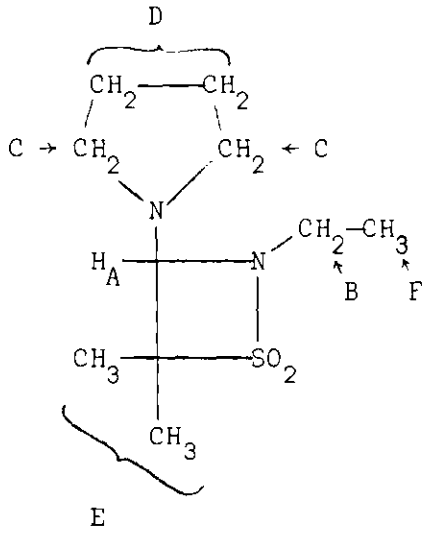
Compound XII was also found to react with the pyrrolidine enamine of isobutyraldehyde giving in good yield 4,4-dimethyl-2-ethyl-3-(N-pyrrolidino)-1,2-thiazetidine-1,1-dioxide (XIX).



XII XIX

*Page 4, this thesis.

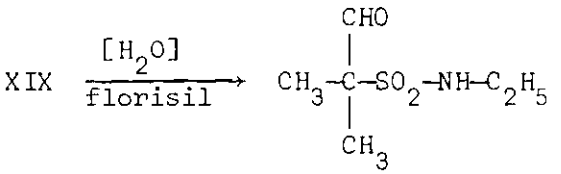
Since attempts to purify XIX for complete analysis were unsuccessful, the structure assigned to XIX is based in large part on its nmr spectrum.



XIX

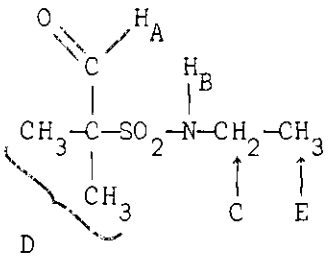
H	τ	mult (J)
A	6.34	s
B	6.78	q (7)
C	7.00-7.49	m
D	8.06-8.38	m
E	8.43	s
F	8.72	t (7)

The chromatography of XIX over florisil effected its hydrolysis to α-(ethylsulfamoyl)isobutyraldehyde (XX). The structure of XX, based largely on its nmr spectrum, confirms the orientation assigned to the



XX

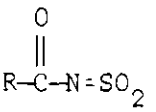
cyclic structure XIX. Compound XX gave a yellow 2,4-dinitrophenylhydrazone with melting point 186.5-87.5°C.



XX

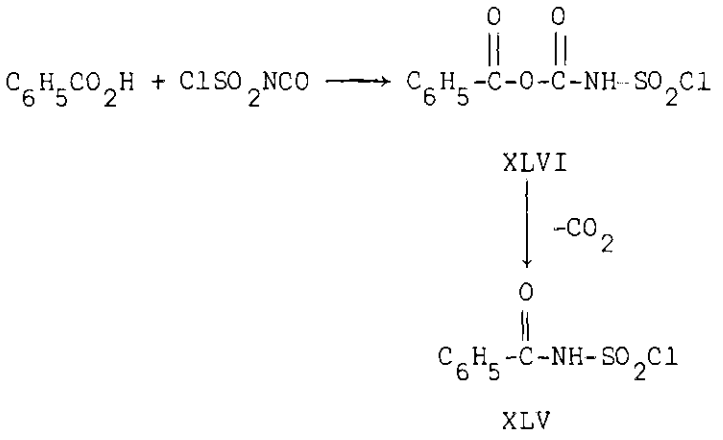
H	τ	mult (J)
A	0.24	s
B	4.32	s
C	6.82	q (7)
D	8.48	s
E	8.83	t (7)

While N-sulfonylethylamine (XII) appeared to have reacted smoothly with strongly nucleophilic olefins such as ketene acetals and enamines, it did not react with ethyl vinyl ether, an olefin of more moderate nucleophilicity In order to extend the scope of reactions of this new heterocumulene, it therefore became desirable to prepare substituted N-sulfonylamines of greater electrophilicity. The placing of a carbonyl group adjacent to the nitrogen of the N-sulfonylamine, to give XLIV, was considered an effective method of increasing electrophilic reactivity.

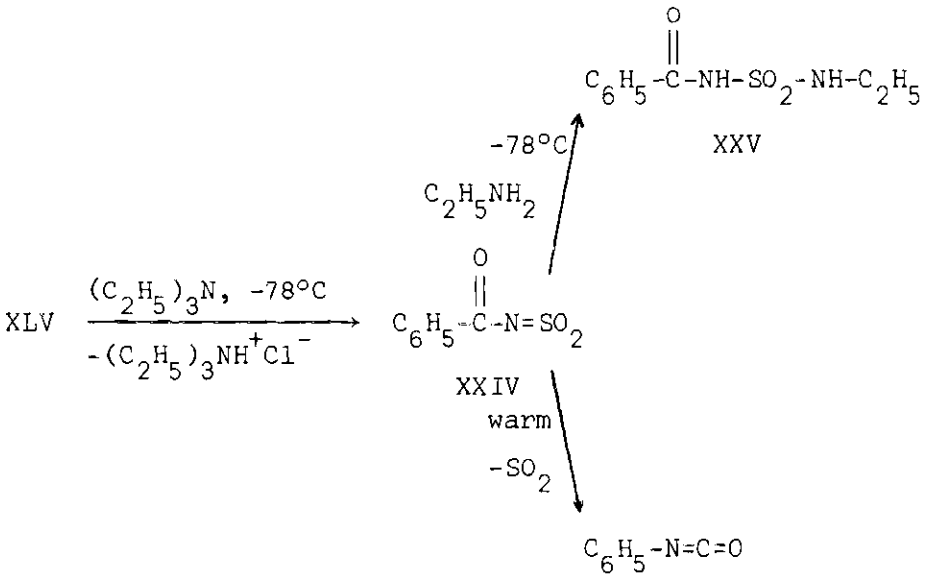


XLIV

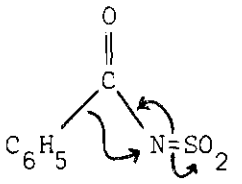
The synthesis of benzoylsulfamoyl chloride had been reported previously (17). When chlorosulfonyl isocyanate was reacted with benzoic acid, the mixed anhydride XLVI was first formed which subsequently at 50°C decarboxylated smoothly to give XLV.



When XLV was mixed with triethylamine in THF solution at -78°C, a quantitative precipitate of triethylamine hydrochloride formed and was collected by filtration. Treatment of the resulting solution of N-sulfonylbenzamide (XXIV) at -78°C with ethylamine afforded N-ethyl-N'-benzoylsulfamide (XXV) in good yield. When the solution of XXIV at -78°C was allowed to warm to room temperature, a rearrangement to



phenyl isocyanate occurred. This reaction may represent an α-elimination of sulfur dioxide, as shown, or may involve the intermediacy of benzoylnitrene.



Generation of XXIV in the presence of ethyl vinyl ether and excess triethylamine gave N-benzoyl-β-ethoxyvinylsulfonamide (XXVI). However, when these same reactants were mixed under conditions of limited triethylamine, the product was 2-benzoyl-3-ethoxy-1,2-thiazetidine-1,1-dioxide (XXVII) resulting from a non-concerted cycloaddition. Recalling the arguments advanced to account for the acyclic product (XV) from the reaction of N-sulfonylethylamine and ketene diethylacetal,* one could propose that XXVI arose through base catalyzed ring-opening of XXVII. Indeed, it was found that XXVII could be converted to XXVI by treatment with triethylamine. In addition to chemical verification of the mechanism leading to the product (XXVI) of the first reaction (excess base), this conversion confirms the orientation of cycloaddition leading to XXVII.

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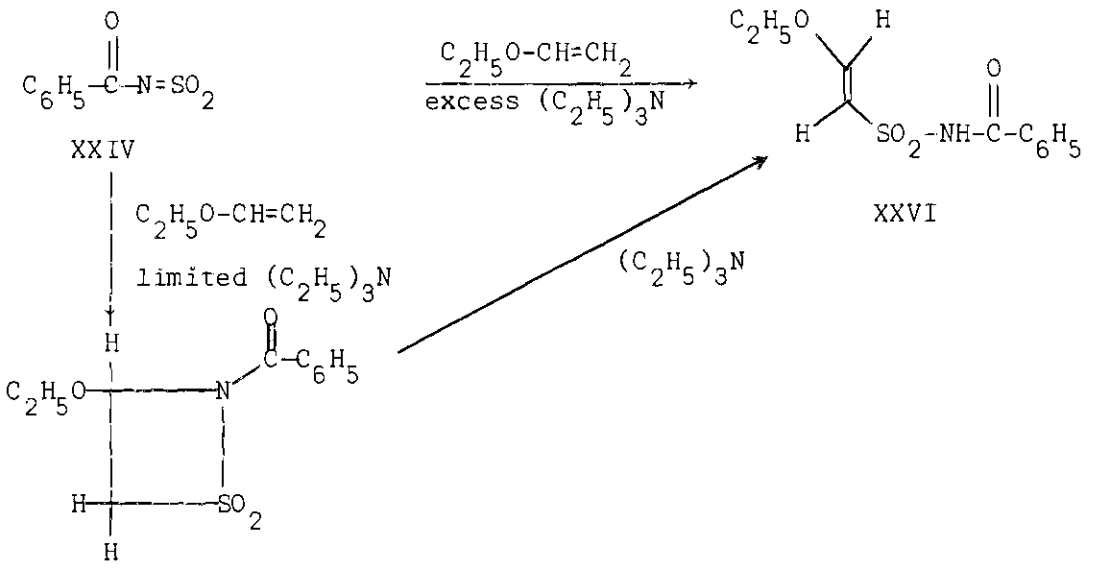
*Pages 31-32, this thesis.



Compound XXVI has been illustrated as being the *trans* isomer, but the possibility cannot be eliminated that it actually possesses *cis* stereochemistry. The coupling constant for the vinyl protons (J = 12 Hz) is intermediate in the ranges expected for *cis* or *trans* disubstituted ethylenes (29).*

In the preparation of XXVII, a trace amount of a compound was isolated for which the 2,3-dihydro-2-ethoxy-6-phenyl-1,4,5-oxathiazine-4,4-dioxide structure (XXVIII) is proposed. Isomeric with XXVII, XXVIII could arise by a concerted orbital-symmetry allowed thermal 2 + 4 cycloaddition (27).

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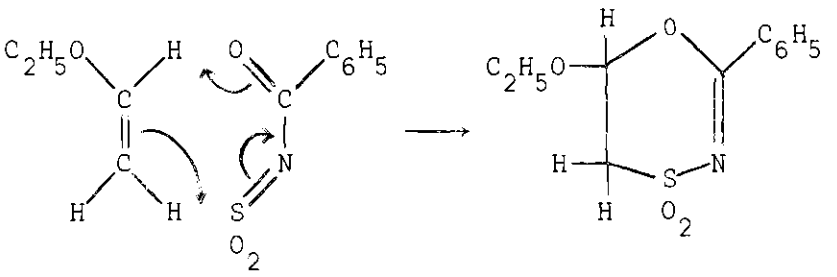
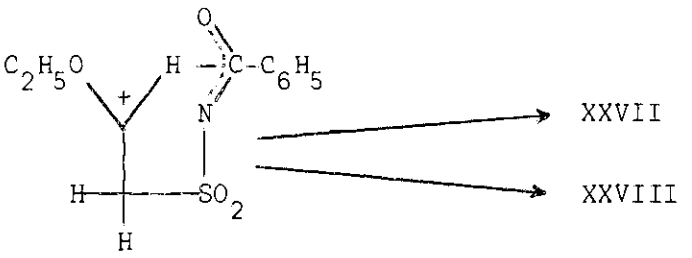
*The *vicinal* olefinic coupling constants for ethyl vinyl ether are J_{trans} = 14 Hz and J_{cis} = 7 Hz.



XXVIII

Alternately, XXVIII may result from ring-closure via a six-centered transition state of the intermediate XLVII.

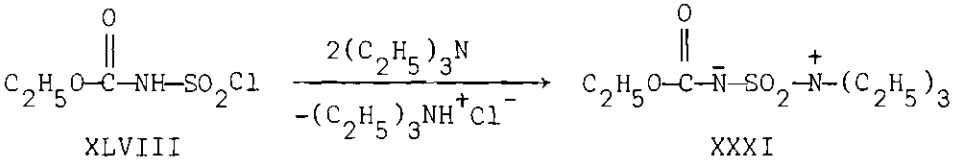


XLVII

Carbethoxysulfamoyl chloride (XLVIII) (19) was prepared by reacting equal molecular amounts of chlorosulfonyl isocyanate and anhydrous ethanol. It was anticipated that the N-sulfonylamine derived from the treatment of XLVIII with base would be less likely to undergo the rearrangement encountered in the case of the benzoyl compound (XXIV) due to the weaker migratory aptitude of ethoxyl as compared to phenyl groups.

When XLVIII was treated with two equivalents of triethylamine, a quantitative yield of precipitated triethylamine hydrochloride was

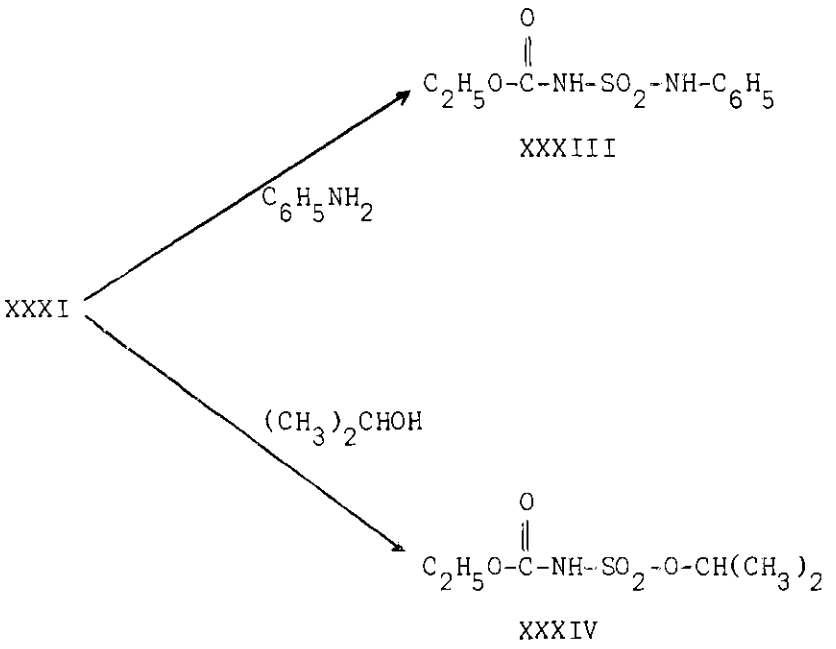
collected. In addition, a colorless crystalline compound was isolated which analyzed for the N-sulfonylamine-triethylamine adduct, (carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester (XXXI).



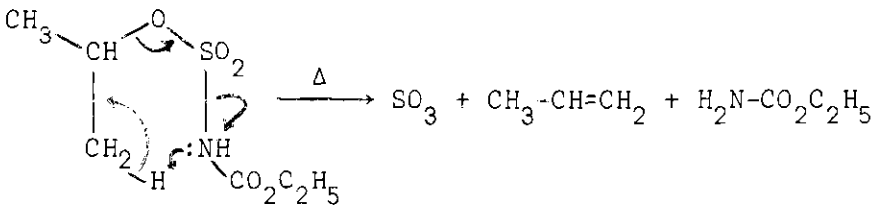
XLVIII XXXI

The structure of XXXI was established by examination of its infrared and nmr spectra and by its subsequent reactions with nucleophiles. The infrared spectrum showed no vibrations characteristic of N-H bonds, and the carbonyl stretching frequency was of unusually low energy (1685 cm^{-1}) as compared to that for a normal urethane C = O linkage (30). The nmr spectrum showed absorptions for one O-ethyl group [quartet (2H) at τ 5.71 and triplet (3H) at τ 8.72] and for three equivalent N-ethyl groups [quartet (6H) at τ 6.71 and triplet (9H) at τ 8.85].

In addition, XXXI reacted with aniline and isopropyl alcohol to give N-carbethoxy-N'-phenylsulfamide (XXXIII) and isopropyl carbethoxysulfamate (XXXIV), respectively.



The sulfamate ester XXXIV underwent a facile elimination at temperatures above 60°C to give ethyl carbamate and two volatile compounds assumed to be sulfur trioxide and propene. These fragmentation products can be envisioned as arising through a six-centered transition state.



XXXIV

Prior to the isolation of XXXI, the non-crystalline sulfene-triethylamine adduct XLIX had been reported (31). Treatment of methyl-

sulfonyl chloride with excess triethylamine in acetonitrile at -40°C gave XLIX, which upon further reaction with trimethylamine led to the crystalline adduct L.

$$2CH_3SO_2Cl + 3(C_2H_5)_3N \xrightarrow[-2(C_2H_5)_3NH^+Cl^-]{CH_3CN,\ -40^\circ C} CH_3SO_2\bar{C}H\text{-}SO_2\text{-}\overset{+}{N}(C_2H_5)_3$$

XLIX

$$\xrightarrow[-(C_2H_5)_3N]{(CH_3)_3N} CH_3SO_2\bar{C}H\text{-}SO_2\text{-}\overset{+}{N}(CH_3)_3$$

L

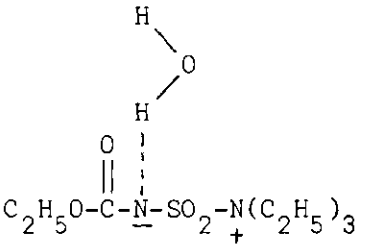
Subsequent to the preparation of XXXI, another N-sulfonylamine-triethylamine adduct (LI) was reported (32). Compound LI was synthesized in a manner similar to XLIX by treating amidosulfonyl chloride (LII) with excess triethylamine in acetonitrile at -40°C.

$$\underset{\text{LII}}{2H_2N\text{-}SO_2Cl} + 3(C_2H_5)_3N \xrightarrow[-2(C_2H_5)_3NH^+Cl^-]{CH_3CN,\ -40^\circ C} \underset{\text{LI}}{H_2N\text{-}SO_2\text{-}\bar{N}\text{-}SO_2\text{-}\overset{+}{N}(C_2H_5)_3}$$

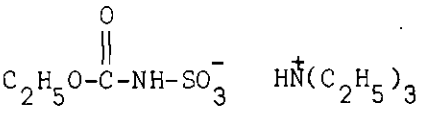
While attempts to use LI in cycloaddition reactions have not been reported, L reacted with enamines and vinyl ethers to give cyclic products (31).

The inner salt XXXI, upon treatment with water, gave a monohydrate (XXXII) which reverted to XXXI on gentle heating under reduced

pressure. This hydrate was considered to be the hydrogen-bonded structure shown and not the product of hydrolysis, LIII, because of the following spectral data. The water protons displayed a single broad



XXXII

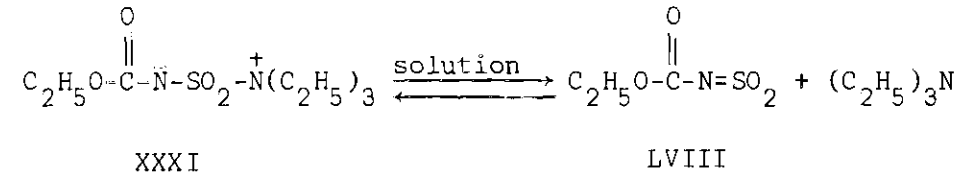


LIII

absorption in the nmr spectrum of XXXII at τ 1.62. The carbonyl absorption for XXXII in the infrared at 1720 cm^{-1} is intermediate in energy between that of the inner salt XXXI (1685 cm^{-1}) and those values found for the carbonyls of compounds* having the grouping $C_2H_5OCONHSO_2$- (1740-1755 cm^{-1}). In addition, XXXII dehydrated under conditions milder than would be expected for the dehydration of LIII. The action of water on XXXI is in contrast to that for L which reportedly underwent hydrolysis (31).

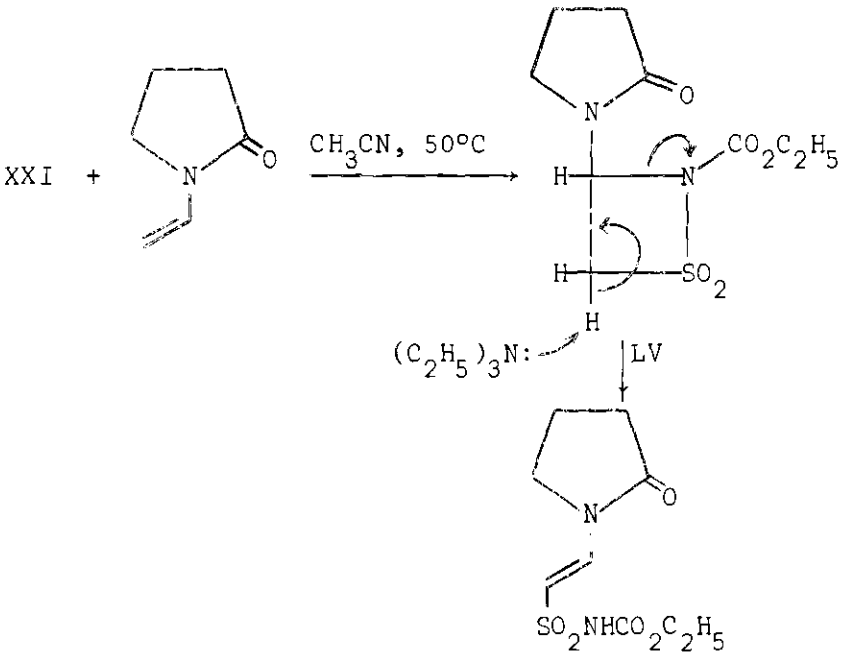
It is possible that the inner salt XXXI exists in solution as an equilibrium mixture of XXXI with ethyl N-sulfonylcarbamate (LVII) and triethylamine. If true, it is reasonable to assume that elevated temperatures should increase the rate of dissociation of XXXI and thus increase the concentration as well as the reactivity of LVII. In fact, it was found that products derived from LVII appeared from reaction of

*These compounds are XXXIII, XXXIV, XXXV and XXXVI.



XXXI LVIII

XXXI at temperatures in the range 50-60°C. For example, when a mixture of XXXI and 1-vinyl-2-pyrrolidinone (LIV) in acetonitrile was allowed to stand for several hours at room temperature, no reaction occurred. However, when the temperature was raised to 50°C, a reaction took place

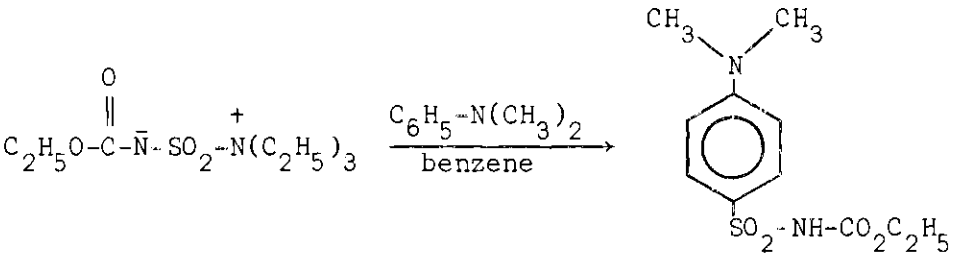


XXXV

providing XXXV in good yield. Compound XXXV may have arisen through a non-concerted cycloaddition providing LV which subsequently underwent triethylamine catalyzed ring-opening.

As in the case of XXVI, XXXV is shown as the *trans* isomer, although the coupling constant for the olefinic protons ($\underline{J}$ = 14 Hz) does not firmly differentiate this possibility from the *cis* system.*

Compound XXXI was capable of electrophilic aromatic substitution with N,N-dimethylaniline. Reaction of XXXI with N,N-dimethylaniline in benzene at ambient temperatures for 16 hours gave N,N-dimethyl-N'-carbethoxysulfanilamide (XXXVI) in 36 per cent yield.



XXXVI

When carbethoxysulfamoyl chloride (XLVIII) was reacted directly with N,N-dimethylaniline, XXXVI was produced in 61 per cent yield. The increased yield of XXXVI might be accounted for by the formation of the inner salt LVI which, because of the reduced basicity of N,N-dimethylaniline compared to triethylamine, would be more reactive than XXXI. Alternately, in the second case the sulfamating agent may be ethyl N-sulfonylcarbamate (LVII).

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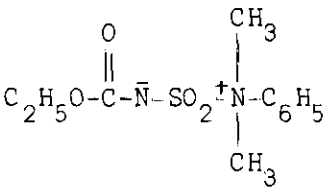
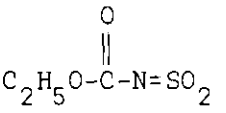
*The *vicinal* olefinic coupling constants for 1-vinyl-2-pyrrolidinone are J_{trans} = 16 Hz and J_{cis} = 9 Hz.

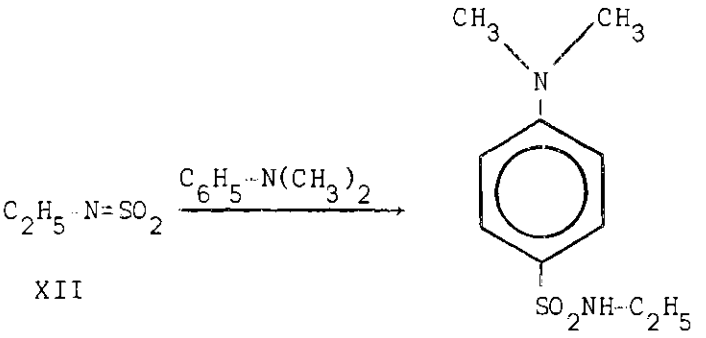


LVI



LVII

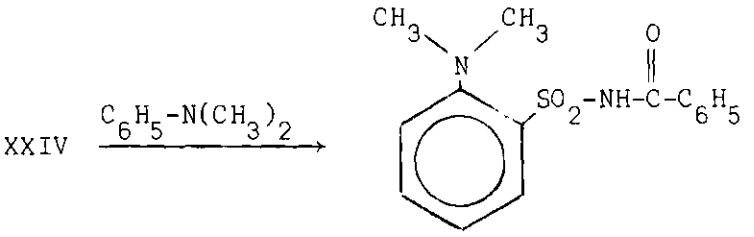
N-Sulfonylethylamine (XII) generated in the presence of N,N-dimethylaniline gave N,N-dimethyl-N'-ethylsulfanilamide (XXIII) in 47 per cent yield.



XII

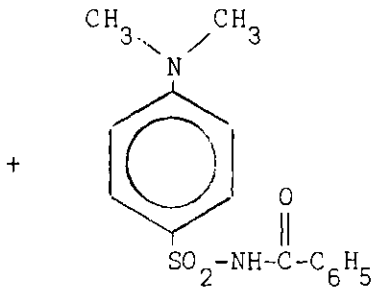
XXIII

In its reaction with N,N-dimethylaniline, N-sulfonylbenzamide (XXIV) gave only a 7.6 per cent over-all yield of a mixture of the ortho (XXIX) and para substituted (XXX) isomers in a ratio of 2:3. Only the para isomer, N,N-dimethyl-N'-benzoylsulfanilamide (XXX), was isolated in the pure state.



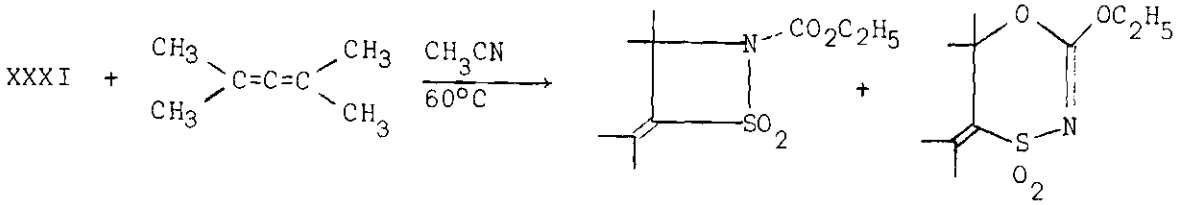
XXIV

XXIX



XXX

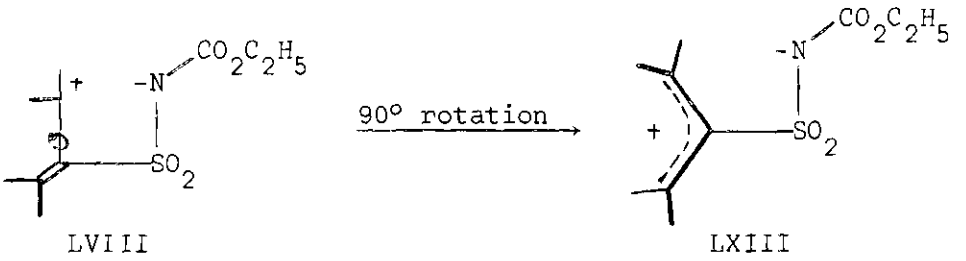
Compound XXXI reacted with tetramethylallene at 60°C in acetonitrile to give a mixture of isomeric four- and six-membered cyclic products: 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidene-1,1-dioxide (XXXVII) and 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine-4,4-dioxide (XXXVIII) in a ratio of 3:17.



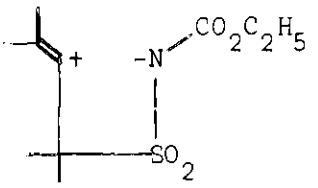
XXXVII

XXXVIII

The infrared and nmr spectra of XXXVII are consistent with the structure shown. The mass spectrum of XXXVII displayed no ions which would establish the orientation of this cycloaddition. Therefore, the orientation proposed is based on the tertiary carbonium ion intermediate LVIII being more stable than the alternate vinyl carbonium ion intermediate LIX.

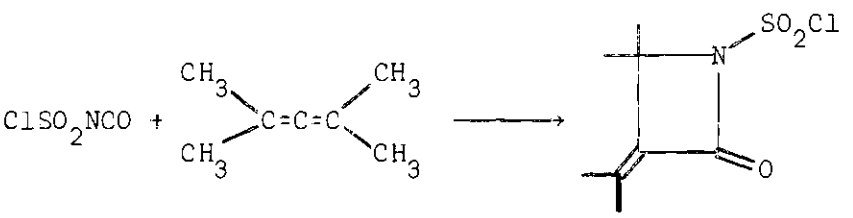


LVIII LXIII



LIX

An argument similar to this was advanced in assigning the structure LX to the adduct formed in the reaction of chlorosulfonyl isocyanate and tetramethylallene (33).

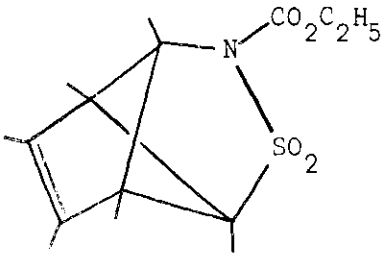


LX

Compound XXXVIII may have been formed through a concerted 2 + 4 thermal cycloaddition* or through a six-centered ring-closure of the long-lived allyl-stabilized intermediate LXIII from the non-concerted addition.

Under similar conditions, XXXI did not react with the less nucleophilic olefin, allene.

Compound XXXI reacted at 60°C with hexamethylbicyclo[2.2.0]-hexa-2,5-diene to give an adduct which displayed nmr spectra (chloroform-d and benzene) showing, in addition to other absorptions, sharp 6-proton singlets at τ 8.27 and 8.75 in $CDCl_3$ (τ 8.49 and 8.73 in benzene). These and the other spectral data** are consistent with the symmetrical structure XXXIXa for the adduct.



XXXIXa

This structural assignment is consistent with others accorded to the reaction products of hexamethylbicyclo[2.2.0]hexa-2,5-diene and other dienophiles (34,35). However, one cannot ignore some recent work (36) which casts doubt on structure XXXIXa and others similar to it (34,35).

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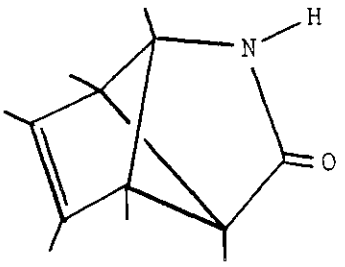
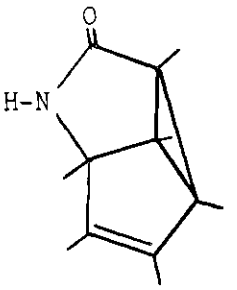
*Page 39, this thesis.

**Page 26, this thesis.

It has been reported that when chlorosulfonyl isocyanate was reacted with hexamethylbicyclo[2.2.0]hexa-2,5-diene, an adduct was obtained which, after hydrolysis of the sulfonyl chloride moiety, displayed in its nmr spectrum sharp 6-proton singlets at τ 8.38 and 8.72 ($CDCl_3$). However, reduction of the double bond in this adduct demonstrated that the vinyl methyls (τ 8.38) were chemically nonequivalent. The hydrogenated adduct displayed in its nmr ($CDCl_3$) three-proton doublets at τ 9.10 and 9.22. These data rule out the symmetrical structure LXI. Compound LXII was proposed as the structure of this adduct on mechanistic stereoelectronic grounds (36). In light of these

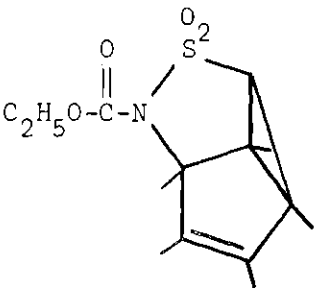


LXI



LXII

results, one must consider the possibility that the adduct XXXIX has a non-symmetrical structure such as XXXIXb.



XXXIXb

CHAPTER IV

CONCLUSIONS

N-Sulfonylamines have been synthesized by the action of triethylamine on sulfamoyl chlorides. N-sulfonylethylamine (XII) and N-sulfonylbenzamide (XXIV) have been prepared in this manner and intercepted in solution by amines to give sulfamides. Compounds XII and XXIV also reacted with nucleophilic olefins to give 1,2-thiazetidine-1,1-dioxides when the reactions were carried out under conditions which did not favor ring-opening. In several cases, ring-openings occurred leading to β-substituted vinylsulfonamides or other acyclic products.

Neither N-sulfonylethylamine (XII) nor N-sulfonylbenzamide (XXIV) could be isolated from solution. Compound XII underwent exothermic polymerization at room temperature in the absence of a trapping agent, while XXIV rearranged to phenyl isocyanate upon standing at room temperature.

(Carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester, (XXXI) was synthesized giving a stable crystalline N-sulfonylamine-triethylamine adduct. Compound XXXI reacted with amines and alcohols as well as with the nucleophilic olefin, 1-vinyl-2-pyrrolidinone. Compound XXXI reacted at 60°C with tetramethylallene to give 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidine-1,1-dioxide (XXXVII) and 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine-4,4-dioxide (XXXVIII). In another reaction at 60°C, XXXI

again acted as a precursor to N-sulfonylurethan (LVII) giving a 1:1 adduct with hexamethyl-bicyclo[2.2.0]hexa-2,5-diene. The structure of this adduct has not been firmly established.

N-Sulfonylethylamine (XII) and (carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester, (XXXI) reacted with N,N-dimethylaniline giving sulfanilamides in fair yields. However, N-sulfonylbenzamide proved to be a poor sulfamating agent for N,N-dimethylaniline.

Portions of this research have been reported previously (37,38).

LITERATURE CITED*

1. A. Wurtz, *Compt. Rend.*, *27*, 242 (1848).

2. W. Lwowski and E. Schriffele, *J. Am. Chem. Soc.*, *87*, 4359 (1965).

3. T. Nagai, K. Yamamoto and N. Tokura, *Bull. Chem. Soc. Jap.*, *40*, 408 (1967).

4. R. Appel and M. Goehring, *Z. anorg. u. allgem. Chem.*, *271*, 171 (1953).

5. H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, 1967.

6. W. D. Emmons in "Heterocyclic Compounds with Three- and Four-membered Rings." A. Weissberger, ed., Interscience Publishers, New York, 1964, p. 978.

7. B. J. R. Nicolaus, E. Bellasio and E. Testa, *Helv. Chim. Acta*, *XLV*, 717 (1962).

8. B. J. R. Nicolaus, E. Bellasio and E. Testa, *ibid.*, *XLVI*, 450 (1963).

9. "Handbook for Authors," American Chemical Society Publications, Washington, D.C., 1967, p. 54.

10. N. C. Hansen, *Acta Chem. Scand.*, *17*, 2141 (1963).

11. *Org. Synthesis*, *23*, 45 (1943).

12. R. L. Hinman and L. Locatell, *J. Am. Chem. Soc.*, *81*, 5655 (1959).

13. S. M. McElvain and M. J. Curry, *ibid.*, *70*, 3781 (1948).

14. F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, 1966, p. 22.

15. G. Opitz, H. Hellmann and H. W. Schubert, *Ann.*, *623*, 112 (1959).

---

*For the complete titles of all journals referred to, see *Chemical Abstracts*, *50*, 1 J (1956).

16. R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1957, p. 111.

17. A. Dorlars in Houben-Weyl's "Methoden der Organischen Chemie," Vol. 8, E. Muller, ed., Georg Thieme Verlag, Stuttgart, Germany, 1952, p. 700.

18. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Molecules," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1965, p. 104.

19. Reference 17, p. 699.

20. R. Graf, German Patent 940,292 (1956); *Chem. Abstr., 52,* 14667c.

21. Belgain Patent 622,214 (1963); *Chem. Abstr., 59,* 12710d.

22. For example, see G. Opitz and M. Kleemann, *Ann., 665,* 114 (1963).

23. Reference 5, pp. 38-9.

24. E. Wedekind and D. Schenk, *Ber., 44,* 198 (1911).

25. Reference 5, p. 286.

26. Reference 5, p. 288.

27. R. Hoffman and R. B. Woodward, *J. Am. Chem. Soc., 87,* 395, 2046 (1965).

28. It has been reported recently that while such 2 + 2 thermal cycloadditions are forbidden to be concerted they may be sterospecific. E. J. Moriconi and J. F. Kelly, *Tetrahedron Letters, 1968,* 1435.

29. Reference 18, p. 99.

30. Reference 18, p. 36.

31. G. Opitz and D. Bucher, *Tetrahedron Letters, 1966,* 5263.

32. R. Appel and R. Helwerth, *Angew. Chem., 79* (21), 937 (1967).

33. E. J. Moriconi and J. F. Kelly, *J. Am. Chem. Soc., 88,* 3657 (1966).

34. W. Schafer and H. Hellmann, *Angew. Chem. Internat. Ed., 6,* 518 (1967).

35. D. M. Lemal and J. P. Lokensgard, *J. Am. Chem. Soc., 88,* 5934 (1966).

36. The author is grateful to Dr. Leo A. Paquette, Ohio State University, for a preprint of the paper on this work. L. A. Paquette, *Tetrahedron Letters, 1968,* in press.

37. G. M. Atkins, Jr. and E. M. Burgess, *J. Am. Chem. Soc., 89,* 2502 (1967).

38. E. M. Burgess and G. M. Atkins, Jr., Paper No. 325, Southeastern Regional Meeting, American Chemical Society, Atlanta, Georgia, November, 1967.

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